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This invention describes a novel bacterium modified to release a foreign DNA under the control of eukaryotic regulatory elements into a foreign organism, organ, tissue, cell line or individual cells after infection of the host. The method of the invention allows a targeted genetic conditioning (TGC) for inducing targeted somatic transgenesis in an animal host where a bacteria comprising a foreign DNA integrated into an episomal vector releases, in the case of infection of a foreign organism, organ, tissue, cell line or individual cells, the foreign DNA under the control of eukaryotic regulatory elements for later transcription and expression, causing transcription and expression of foreign DNA under the foreign protein in the location. The method is used for induced somatic gene therapy, immunological protection against microbes or protection against tumours. Listeria monocytogenes can be modified so that it has reduced pathogenicity in animals and can produce foreign proteins that are then secreted into, e.g. milk. Examples of where the method are useful, include treatment of cystic fibrosis (by manipulation of an airborne bacteria), treatment of beta-thalassemia by ex vivo modification of a haematopoietic cell to contain beta-globulin, for treatment of thurler syndrome by infection of CD34+ cells of the bone marrow with an alpha-L-iduronidase gene and also to treat Fanconi's anaemia with a group complementation gene. The method does not require genetic transformation/modification of the organism requiring gene therapy. The method allows for safe and ethical gene therapy in an organism. The expression of a therapeutic foreign protein by a bacteria that infects an animal is advantageous in that the expression can be tissue- or organ-
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ALIGNMENTS

RESULT 1 AAR91823

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(a) peptides which bind the SH3 domain of Cortactin; (b) peptides which bind the middle SH3 domain of Nck; (c) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which bind the SH3 domain of Src; (e) peptides which could be used to modulate the Sh3 domain. The peptides can also be used to activate Src or Src-related protein tyrosine kinases, to stimulate the immune response by increasing the production of certain lymphokines, e.g. tumour necrosis factor-alpha and interleukin-1, or to deliver a conjugated molecule to certain C cellular compartments containing Src or Src related proteins
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420	ANIDDTQYLAAKRAIRTVFGTEPDMIRDGSTIPIAKMFQEIVHKSVVLIPLGAVDDGEHS 479
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SHK -	ANIDDTQYLAAKRAIRTVFGTEPDMIRDGSTIPIAKMFQEIVHKSVVLIPLGAVDDGE	421	Db
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)EP 359	VPLTEEBINTYKAIHLDLEEYRNSSRVEKFLFDTKEEILMHLWRYPSLSIHGIEGAFDEP	300	γQ

Search completed: February 17, 2005, 17:32:29 Job time : 0.001 secs

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Title: Perfect Sequence Scoring table score: us-10-036-342-57 2623 1 MDPKLGRMAASLLAVLLLLL 0.5 .NYIEGTKLFAAFFLEMAQLH

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148

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number 0f hits satisfying chosen parameters:

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us-09-621-976-3957:*

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SUMMARIES

Result سا Score 607.5 Query Match Length 23.2 148 DB us-09-621-976-3957 Įþ Description

ALIGNMENTS

RESULT 1 us-09-621-976-3957

Query Match 23.2%; Best Local Similarity 96.9%; Matches 124; Conservative Score 607.5; Pred. No. 0; 0; Mismatches DB 1 ω •• Length 148; Indels Gaps

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멍 Ş 121 120 SDPTXXTV SDPTKGTV 127 128

Search completed: Job time : 0.001 : February 17, 2005, 17:08:51

Listeria monocytogenes (strain EGD-e)
C;Species: Listeria monocytogenes
C;Date: 27-Nov-2001 #sequence_revision 27-Nov-2001 #text_change 09-Jul-2004
C;Accession: AB1108
R;Glaser, P.; Frangeul, L.; Buchrieser, C.; Amend, A.; Baquero, F.; Berche, P.;
Bloecker, H.; Brandt, P.; Chakraborty, T.; Charbit, A.; Chetouani, F.; Couve,
E.; de Daruvar, A.; Dehoux, P.; Domann, E.; Dominguez Bernal, G.; Duchaud, E.;
Durand, L.; Dussurget, O.; Entian, K.D.; Fsihi, H.; Garcia-Del Portillo, F.;
Garrido, P.; Gautier, L.; Goebel, W.; Gomez-Lopez, N.; Hain, T.; Hauf, J.;
Jackson, D.; Jones, L.M.; Karst, U.
Science 294, 849-852, 2001
A;Authors: Kreft, J.; Kuhn, M.; Kunst, F.; Kurapkat, G.; Madueno, E.;
Maitournam, A.; Mata Vicente, J.; Ng, E.; Nordsiek, G.; Novella, S.; de Pablos,
B.; Perez-Diaz, J.C.; Remmel, B.; Rose, M.; Rusniok, C.; Schlueter, T.; Simoes,
N.; Tierrez, A.; Vazquez-Boland, J.A.; Voss, H.; Wehland, J.; Cossart, P.
A;Title: Comparative genomics of Listeria species.
A;Reference number: AB1077; MUID:21537279; PMID:11679669
A;Status: preliminary
A;Rosidues: 1-379 <GLA>
A;Cross-references: UNIPROT:09ZEYO, GB:NC_003210; PIDN:CAD00792.1;
PID:g16409630; GSPDB:GN00177
A;Experimental source: strain EGD-e Title: Perfect score: Sequence: Minimum Maximum Result Scoring table Run Searched: OM protein Database Post-processing: No. on: number score s Pred. DB Bd 211.5 Score geg geg No. is the number of results predicted by chance to have greater than or equal to the score of the result being posterived by analysis of the total score distribution. 0f protein length: length: hits BLOSUM62 Gapop 10.0 Query Match Minimum Maximum Listing us-10-036-342-57 2623 1 MDPKLGRMAASLLAVLLLLL. Η February ab1108.pir2:* seqs, 8.1 Copyright satisfying search, Length 0 2000000000 379 Match Match first 17, 379 residues 2005, DB using Gapext μ 100**៖** 45 នា 80 chosen AB110 G summaries 38 16:21:08 0 . 5 **ALIGNMENTS** SUMMARIES mode1 parameters: ; Search time 0.001 (without alignments) 192.153 Million cell .NYIEGTKLFAAFFLEMAQLH \vdash Description succinyldiaminop updates/sec Seconds printed ρ Couve, Pablo: Simoes

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- hypothetical protein YFR044c - yeast (Sacc N;Alternate names: hypothetical protein F006 C;Species: Saccharomyces cerevisiae C;Date: 02-Sep-1995 #sequence_revision 19-Oc C;Accession: S56299; S62255; S63791 R;Murakami, Y.; Naitou, M.; Hagiwara, H.; Sl R; Sasanuma, M.; Tsuchiya, Y.; Soeda, E
                                                                                                                                              S.I.; Sabaname,
Tashiro, H.; Eki, T.
submitted to the EMBL Data L
A; Description: Analysis of t
Saccaromyces cerevisiae.
Saccaromyces cerevisiae.
                              R; Murakami, Y.
submitted to the EMBL
A; Reference number: So
A; Accession: S62255
A; Molecule type: DNA
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A; Cross-references: UNIPROT: P43616; EMBL: D50617;
PID:d1009924; PID:g836799; MIPS:YFR044c
R; Murakami, Y.
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: Analysis of a 36.2 kb DNA sequence including the some VI from Saccharomyces cerevisiae.
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C;Accession: S43745
R;Lopez, M.; Nicaud, J.; Vergnolle, C.; Kader, J.; Banlsubmitted to the EMBL Data Library, July 1993
A;Description: A phospholipid transfer protein is requitransition in the yeast Yarrowia lipolytica.
A;Reference number: S43745
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A;Cross-references: UNIPROT:P45816; EMBL:L20972; NID:g.
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A;Gene: SEC14
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TISSUE=Brain;
Chen J.M., Barrett A.J.;
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RA Hopkins R.F., Jordan H., Moore T., Max S.I., Wang J., Hsieh F.,
RA Distchemko L., Marusina K., Farmer A.A., Rubin G.M., Heng L.,
Staplaton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA Staplaton M., Soares M.B., Bonaldo M.F., Casavant T.L., Scheetz T.E.,
RA Brownstein M.J., Undin T.B., Toshiyuki S., Carninci P., Prange C.,
RA Raha S.S., Loquelano N.A., Peters G.J., Males J.A., Gunardne P.H.,
RA Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.M.,
RA Richards S., Worley K.C., Hale S., Garcia A.M., Gay L.J., Hulyk S.M.,
RA Willalon D.K., Muzny D.M., Sodergran E.J., Lu X., Gibbs R.A.,
RA Wilting M., Madan A., Young A.C., Shevhenko Y., Bouffard G.G.,
RA Rodriguez A.C., Grimwood J., Schmutz J., Wyerz R.M.,
RA Rodriguez A.C., Grimwood J., Schmutz J., Wyerz R.M.,
RA Schmerch A., Schein J.E., Jones S.J.M., Marra M.A.;
C. Gereration and initial analysis of more than 15,000 full-length human
RT and mouse cDNA sequences. ",
Proc. Natl. Acad. Sci. U.S.A. 99:16499-16593 (2002).
Proc. Natl. Acad. Sci. U.S.A. 99:1649-16593 (2002).
Proc. Natl. Acad. Sci. U.S.A. 99:1649-16593 (2002).
Proc. Interpolate of Bioinformatics and the Brib outstation tits
cut by non-profit institutions as long as its content is in no way
modified and this statement is not removed. Usage by and for commercial
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T 05-JUL-2004 (TrEMBLrel. 27, Last sequence update)

T 05-JUL-2004 (TrEMBLrel. 27, Last sequence update)

T 05-JUL-2004 (TrEMBLrel. 27, Last sequence update)

E Hypothetical protein FLJ16195.

S Homo sapiens (Human).

C Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;

Mammalia; Eutheria; Primates;

C Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;

K NCBL_TaxID=9606;

N [1]

P SEQUENCE FROM N.A.

C TISSUE=Thalamus;

Ota T., Nakagawa S., Senoh A., Mizuguchi H., Inagaki H., Sugiyama T.,

A Irie R., Otsuki T., Sato H., Wakamatsu A., Ishii S., Yamamoto J.,

A Irie R., Otsuki T., Sato H., Wakamura Y., Sekine M., Kimura K.,

A Yamashita H., Matsuo K., Nakamura Y., Sekine M., Kikuchi H., Kanda K.,

A Yamashita H., Matsuo K., Nakamura Y., Sekine M., Kikuchi H., Kanda K.,

A Yamashita H., Murakawa K., Kanehori K., Takahashi-Fujii A., Oshima A.,

Sugiyama A., Kawakami B., Suzuki Y., Sugano S., Nagahari K.,

A Masuho Y., Nagai K., Isogai T.;

L Submitted (MAR-2004) to the EMBL/GenBank/DDBJ databases.

R EMBL; AK131263; BAD18441.1; -.

SEQUENCE 171 AA; 18880 MW; 20816D6D8F214688 CRC64;
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Scoring table:

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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

Result No. ۲ S core 766 Query
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ALIGNMENTS

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Query Match Best Local S Matches 148 ch 29.2%; l Similarity 100.0%; 148; Conservative Score 766; DB; Pred. No. 0; 0; Mismatches 0; DB <u>ب</u> 0 Length 171; Indels **.** Gaps

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